The Association of Aortic Valve Pathology with Renal Resistive Index as a Kidney Injury Biomarker

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Abstract

Background—Acute kidney injury (AKI) is a common serious complication following cardiac surgery. Doppler-determined renal resistive index (RRI) is a promising early AKI biomarker in this population. However, the relationship between aortic valve pathology (insufficiency and/or stenosis) and RRI is unknown. This study aimed to investigate RRI variability related to aortic valve pathology.

Methods—In a retrospective review of cardiac surgery patients, RRI and aortic valve pathology were assessed prior to cardiopulmonary bypass using transesophageal echocardiography. Aortic valve status was categorized into four subgroups: *normal* (insufficiency and stenosis, none/trace/mild), *insufficiency* (insufficiency, moderate/severe; stenosis, none/trace/mild), combined *insufficiency/stenosis* (insufficiency and stenosis, moderate/severe), or *stenosis* (insufficiency, none/trace/mild; stenosis, moderate/severe). RRI, and time-matched hemodynamic and Doppler measurements were compared among subgroups.

Results—Of 175 patients, 60 had aortic valve pathology (16 insufficiency, 18 insufficiency/ stenosis, 26 stenosis). Compared to the normal subgroup, patients with aortic insufficiency had lower diastolic blood pressure and trough renal Doppler velocities, and higher RRI (0.77 vs 0.69; p<0.001); patients with combined insufficiency/stenosis also had higher RRI (0.72 vs 0.69, p=0.042).

Conclusions—Patients with aortic insufficiency and combined insufficiency/stenosis had higher median RRI values compared to normal patients. For these individuals, diastolic flow differences related to AI may explain why their *pre-surgery* RRI values often exceeded *postoperative* thresholds typically associated with AKI. Strategies to account for the potentially confounding

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effects of aortic insufficiency on renal flow patterns, independent of renal injury, may add to the value of RRI as an early AKI biomarker.

Graphical Abstract
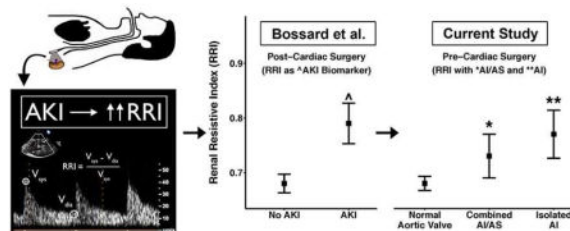
Classifications

Kidney; renal function failure; dialysis; Echocardiography; Cardiac; Surgery; complications; Ultrasound

Acute kidney injury (AKI) is a common and serious complication of cardiac surgery associated with significant morbidity and mortality.[1] Recognition of AKI is often delayed up to 48 hours postoperatively due to reliance on serum creatinine for diagnosis.[2] A search for earlier AKI biomarkers is, therefore, underway.[2] In this regard, there is considerable interest in the Doppler-determined renal resistive index (RRI; Figure 1) using transabdominal ultrasound or transesophageal echocardiography (TEE).[3–8] As an index of renal arterial pulsatility, RRI elevation that exceeds a critical value (e.g., 0.74[3]) may reflect increased renal intracapsular pressure due to AKI.[9, 10] During cardiac surgery, TEE-determined elevation of RRI after separation from cardiopulmonary bypass (CPB) correlates with subsequent AKI diagnosis.[4, 7] Similarly, transabdominal-determined RRI predicts AKI when measured in critically ill patients[5] and soon after various surgical procedures.[3, 6, 8] However, the potential for hemodynamic effects of heart valve abnormalities such as aortic insufficiency (AI) or stenosis (AS) to confound the value of RRI as a biomarker, independent of AKI, is poorly understood.

Serious aortic valve pathology, which may affect renal artery blood flow, is a common indication for cardiac surgery.[11, 12] Consequently, better understanding of the relationship among the various types of aortic valve pathology and RRI may add to its value as an AKI biomarker. Therefore, we hypothesized that patients with and without aortic valve pathology have different intraoperative RRI values prior to surgery-related renal insult (i.e., pre-CPB).

Patients and Methods

Study Population

After Institutional Review Board approval, a retrospective review was conducted using prospectively collected data from the Duke Anesthesiology TEE Database and Electronic Medical Record (Epic Systems, Verona, WI). Since RRI determination was introduced as an optional requirement during the study period, a subset of cardiac surgery patients was available for analysis.

Subjects included patients   18 years old who underwent cardiac surgery requiring CPB between 7/1/2013 and 7/10/2014 at Duke University Medical Center (Durham, NC) for whom pre-CPB TEE aortic valve evaluation and renal blood flow measurements were documented. Exclusion criteria included: missing pre- or post-operative creatinine; chronic kidney disease or recent AKI (preoperative estimated creatinine clearance <60 mL/min [Cockroft-Gault]); non-sinus rhythm during RRI acquisition; and renal Doppler images deemed poor quality by blinded reviewers.

Intraoperative Ultrasound Imaging and Post-Hoc Assessment

A comprehensive examination using a multiplane TEE probe (Philips X7-2t; Philips iE33, Andover, MA) is routine prior to, and after, CPB at the reference institution. The examination is performed by an adult cardiothoracic anesthesiology fellow with an attending anesthesiologist certified in advanced peri-operative TEE by the National Board of Echocardiography (Advanced PTEeXAM). Pre-CPB TEE examinations were selected *a priori* for two primary reasons: to (1) maximize the range of uncorrected aortic valve abnormalities, and (2) minimize the effects on RRI of any procedural factors (e.g., surgery-related renal insult).

Assessment of Aortic Valve Status—Severity of AI and AS (none/trace/mild/ moderate/severe) was reported in the TEE Database using standardized criteria.[13, 14] For analysis, subjects were grouped by aortic valve status: *normal* (AI and AS, none/trace/mild), *insufficiency* (AI, moderate/severe; AS, none/trace/mild), combined *insufficiency/stenosis* (AI and AS, moderate/severe), or *stenosis* (AI, none/trace/mild; AS, moderate/severe).

Assessment of Pre-CPB Renal Resistive Index—Left renal artery Doppler velocity images were obtained using a transgastric approach.[15] Seven TEE-certified cardiothoracic anesthesiologists (blinded to aortic valve status) re-reviewed de-identified renal images to determine RRI values. Doppler images were distributed among reviewers, for whom intra- and inter-rater reliability for RRI determination was previously confirmed.[4] Renal arterial peak systolic (V_{sys}) and trough diastolic (V_{dia}) velocities were measured for all suitable cardiac cycles (1–3); RRI was calculated for each cycle (Figure 1), and averaged for each subject.

Additional Measurements

Hemodynamic Parameters—Intra-arterial (radial or femoral) blood pressure parameters (systolic [SBP], diastolic [DBP], and mean arterial pressure) both at baseline (pre-induction) and time-matched to RRI determination were obtained from the medical record. Values that were likely erroneous (related to instrument error or line flushes), were excluded if they fell outside pre-defined ranges: SBP 40–250, DBP 15–200, mean arterial pressure 30–250, and pulse pressure (PP) >5 mmHg. Baseline measures were the median of the first 5 intraoperative values. Time-matched measures were the mean of values within 1 minute of RRI acquisition.

Renal Function Parameters—Serum creatinine was measured using the Jaffe technique (UniCel DxC-800, Beckman Coulter, Brea, CA). Per institutional protocol, creatinine was

measured preoperatively and at least daily postoperatively. If multiple assessments occurred on one day, the earliest was utilized. Preoperative creatinine was defined as the value closest to, but not on, the day of surgery within 5 days preoperatively. Due to lack of accurate urine output data for all patients, AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on creatinine.[2]

Statistical Analysis

Statistics are presented as median (Q1–Q3) or frequency (%). Patient and procedural characteristics were compared between aortic valve subgroups using the Kruskal-Wallis or Chi-Squared test.

In the primary analysis, pre-CPB RRI was compared among subgroups utilizing the Kruskal-Wallis test. Due to small subgroup sizes, *post-hoc* pairwise comparisons were performed using two-sample t-tests with permutation and Benjamini-Hochberg adjustment to control false-discovery rate at 0.05.

Secondary analyses comparing time-matched hemodynamic and Doppler parameters among subgroups were performed using the same methodology as the primary analysis. The relationship between RRI and aortic valve status was further examined with multiple linear regression adjusted for age, sex, DBP, PP, left ventricular ejection fraction, and postoperative AKI status.

Significance was defined as $p < 0.05$ (R version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 175 patients meeting inclusion criteria (Figure 2), 60 had documented aortic valve pathology (16 AI, 18 AI/AS, 26 AS). Patient and procedural characteristics were similar to those observed in other populations (Table 1).[16] Baseline differences among aortic valve subgroups included age, left ventricular ejection fraction, and DBP. Procedural factors (related to events following RRI measurement) also varied, including surgery type, and duration of aortic cross-clamp application, but rate and severity of AKI were similar among subgroups (Table 2).

Renal Resistive Index

Aortic valve pathology was strongly associated with variability in RRI (p=0.0003; Table 3). In *post-hoc* analysis when compared to the normal subgroup median RRI was elevated in the AI (0.77 vs 0.69; adjusted p<0.001) and AI/AS (0.72 vs 0.69; adjusted p=0.042) but not the AS subgroup (adjusted p=0.38; Figure 3).

Time-Matched Hemodynamic and Doppler Parameters

To better understand our primary observation regarding the association of RRI with aortic valve pathology, Doppler components of RRI were compared among subgroups (Table 3). V_{sys} was similar (p=0.87), while V_{dia} varied significantly among subgroups (p=0.006). In *post-hoc* analysis, median V_{dia} was lower with AI compared to both the normal (0.58 vs

0.84; adjusted p=0.03; Figure 4B) and AS subgroups (0.58 vs 1.01; adjusted p=0.03). Similarly, there was no difference in time-matched SBP among subgroups (p=0.80) while a difference existed in time-matched DBP (p=0.007). In *post-hoc* analysis, median time-matched DBP was lower in the AI subgroup compared to both the normal (53 vs 62; adjusted p=0.023; Figure 4A) and AS subgroups (53 vs 59; adjusted p=0.035). In a multiple linear regression model adjusted for age, sex, time-matched DBP and PP, left ventricular ejection fraction, and postoperative AKI status, only isolated AI remained associated with elevation in RRI (0.06, 95% CI [0.02, 0.10]).

Comment

In this retrospective review of cardiac surgery patients, we confirmed variation in RRI associated with aortic valve pathology that preceded any potential renal insult from the surgical procedure (i.e., pre-CPB). Specifically, we found that RRI values in the subgroups with AI and combined AI/AS were elevated compared to normal patients. Importantly, these elevations with AI (0.08 units) and AI/AS (0.03 units) caused *pre-surgery* RRI values to considerably overlap with *post-procedure* thresholds previously associated with AKI (Figure 5). Notably, AKI rates in the AI and AI/AS subgroups were not different from the normal subgroup (Table 2). Hemodynamic and Doppler analyses expose the components of RRI estimation contributing to this observation. Time-matched DBP and V_{dia} were lower in patients with AI but not with other aortic valve pathologies. These findings suggest that the value of, and thresholds for, RRI as an early AKI biomarker may be further improved with appropriate consideration of aortic valve pathology.

Although no previous reports have explored the relationship between aortic valve pathology and RRI, one study involving similar hemodynamic perturbations is informative to compare with the current investigation. Sinning and colleagues noted elevated RRI in patients with moderate/severe *paravalvular leaks* following transcatheter aortic valve replacement (TAVR) [17]. RRI was 0.17 units higher in patients with moderate/severe leaks relative to others. While our findings are consistent with those of Sinning et al., and similar hemodynamic abnormalities (lower DBP and V_{dia}) likely underpin elevated RRI in both settings, notable differences between the studies deserve mention. The greater magnitude of RRI elevation with paravalvular leak vs. isolated AI (0.17 vs. 0.08) may be related to larger regurgitant volumes with the former condition. However, the *post*-procedure timing of RRI measurement by Sinning et al. complicates comparison of the two studies. AKI is a recognized complication of TAVR[18] and is inextricably inserted into *post-procedure* consideration of the effects of paravalvular leak on RRI estimation. This is particularly relevant since AKI risk may differ between patients with and without paravalvular leak. Post-TAVR paravalvular leaks occur more often with calcified valves[19], and additional contrast dye may be required to image a leak, both presumably raising the risk for AKI. Furthermore, higher AKI risk may also be accompanied by the consequences of acute paravalvular leak on perfusion in the setting of renal swelling, whose implications for the evolution of a renal injury are unknown. Such potential confounding effects are not equivalent between studies and it is unlikely they are fully accounted for by adjustment for comorbidities and AKI status. Nonetheless, the most pertinent observation from both studies is that regurgitant aortic lesions are associated with elevated RRI values that overlap

importantly with the range associated with AKI (Figure 5). In the current study, elevated RRI values appear to be hemodynamic "artifacts" of aortic insufficiency, rather than related to any renal insult, and likely confound the value of RRI as an early AKI biomarker.

Our analysis is limited by its retrospective nature. However, the variables utilized involve data electronically transferred to the medical record as part of regular clinical care. Furthermore, blinded re-analysis of prospectively collected TEE images by certified experts should eliminate potential bias in interpreting RRI in relation to existing valve pathology. The small subgroup sizes limit statistical power for comparisons. However, we observed significant associations using empirical p-values obtained using permutation and adjusted for multiple comparisons. Naturally, patients with aortic valve pathology were more likely to be undergoing aortic valvular procedures, associated with varying duration of aortic cross-clamp time. Additionally, as expected, patients with aortic valve pathology were older, and those with AI had lower baseline DBP (Table 1). In order to address the inhomogeneity of such variables, including some that are confounded with RRI (e.g., age, PP), [20] we included an adjusted analysis.

Hemodynamic factors that both affect RRI and are associated with AI could potentially confound our study findings. Variation in the use of radial vs. femoral arterial catheters was not assessed, and wider PP with the latter could vary among groups. However, we have no reason to suspect there was systematic variation in the arterial catheter site across subgroups. Hypertension is associated with RRI variation in some studies, and a reported history of hypertension in our sample was (non-significantly) higher in the AI than other subgroups (Table 1).[21–23] However, the relationship between RRI and hypertension is complex; although RRI is *not* elevated in patients with primary essential hypertension relative to unaffected patients, RRI does differentiate treatment-resistant from treatment-responsive hypertension.[21–23] Since these distinguishing factors are not included in the hypertension documentation available for the current study, we conducted subanalyses to further assess the potential for hypertension to have introduced bias into our primary finding. As previously reported in general populations, patients with (n=53) and without (n=62) a diagnosis of hypertension (from our normal aortic valve subgroup) had very similar RRI values (0.70 vs. 0.68, p=0.33)[21]. Furthermore, a primary re-analysis limited to patients with a history of hypertension (AI, n=12 vs normal valve, n=53) continues to demonstrate a significant difference in RRI (0.78 vs 0.70, p=0.001). Lastly, preoperative proteinuria was not significantly different among subgroups (Table 1). While these analyses do not completely eliminate concerns, we believe they provide reassurance that hypertension is not exhibiting a major confounding effect. Nonetheless, the current study represents the only assessment of aortic valve pathology and its relationship with RRI, including observations that may enhance the value of RRI as an AKI biomarker.

The implications of predictable baseline variation in RRI that could confound its value as a marker of renal insult are worthy of speculation. First, since these observations are predictable, RRI may be amenable to adjustment as a strategy to enhance its value as an early AKI biomarker. No published AKI biomarker studies have integrated adjustment for aortic valve status into their RRI estimation [3, 7, 8], yet even without adjustments RRI is associated with AKI in these cohorts, while such valve lesions likely exist among them.

Accounting for aortic valve status may, in fact further enhance the value of RRI as an AKI biomarker by addressing previously unexplained variability. Further investigations are essential to validate refinements accounting for aortic insufficiency in RRI estimation for AKI prediction. For example, data from the current study suggests that adjusting RRI downward by 0.08 for subjects with moderate/severe AI and by 0.03 for subjects with AI/AS may account for these valvular pathologies. Unfortunately, validation of an approach to improve RRI as an AKI biomarker through "adjustment" is not possible using this cohort since the post-CPB valve status of this subset typically involves valve replacement. Until such validation is complete findings from the current and other studies suggest that RRI should be used with caution as an AKI biomarker in the context of aortic regurgitant lesions. In this regard, our AI subgroup findings align with the abovementioned TAVR report [17], but also analyses in *ex-vivo* perfusion systems and human subjects showing associations between systemic hemodynamics and RRI similar to the current investigation.[20, 24] Finally, as an AKI biomarker, RRI may benefit from a search for other factors that confound its value and are amenable to adjustment. Such information may be useful at the bedside or within decision support tools to make an already valuable biomarker potentially even more useful. This is particularly relevant for cardiac surgery patients given the routine use of intraoperative TEE, and that other early AKI biomarker candidates (e.g., neutrophil gelatinase-associated lipocalin) are more expensive and less immediately available, yielding information with several hours delay following renal insult relative to intraoperative RRI [25].

In summary, in cardiac surgery patients, pre-procedure intraoperative RRI values determined by TEE were elevated in patients with isolated AI and combined AI/AS compared to those with normal valvular function, likely related to effects on diastolic renal blood flow. Regarding RRI as an AKI biomarker, these observations suggest that regurgitant aortic lesions create a hemodynamic "artifact" unrelated to renal insult that may confound its value. Given the common occurrence of aortic valve pathology in patients undergoing cardiac surgery and the need for reliable early AKI biomarkers, additional research is needed to better understand this issue. Furthermore, if the role of aortic pathology and other potential confounders can be clarified, such improvements may add value to RRI as an early AKI biomarker.

Abbreviations

AI	Aortic insufficiency
AKI	Acute kidney injury
AS	Aortic stenosis
CPB	Cardiopulmonary bypass
DBP	Diastolic blood pressure
KDIGO	Kidney Disease: Improving Global Outcomes
PP	Pulse pressure

RRI	Renal resistive index
SBP	Systolic blood pressure
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiography
V_{sys}	Peak systolic velocity
V_{dia}	Trough diastolic velocity

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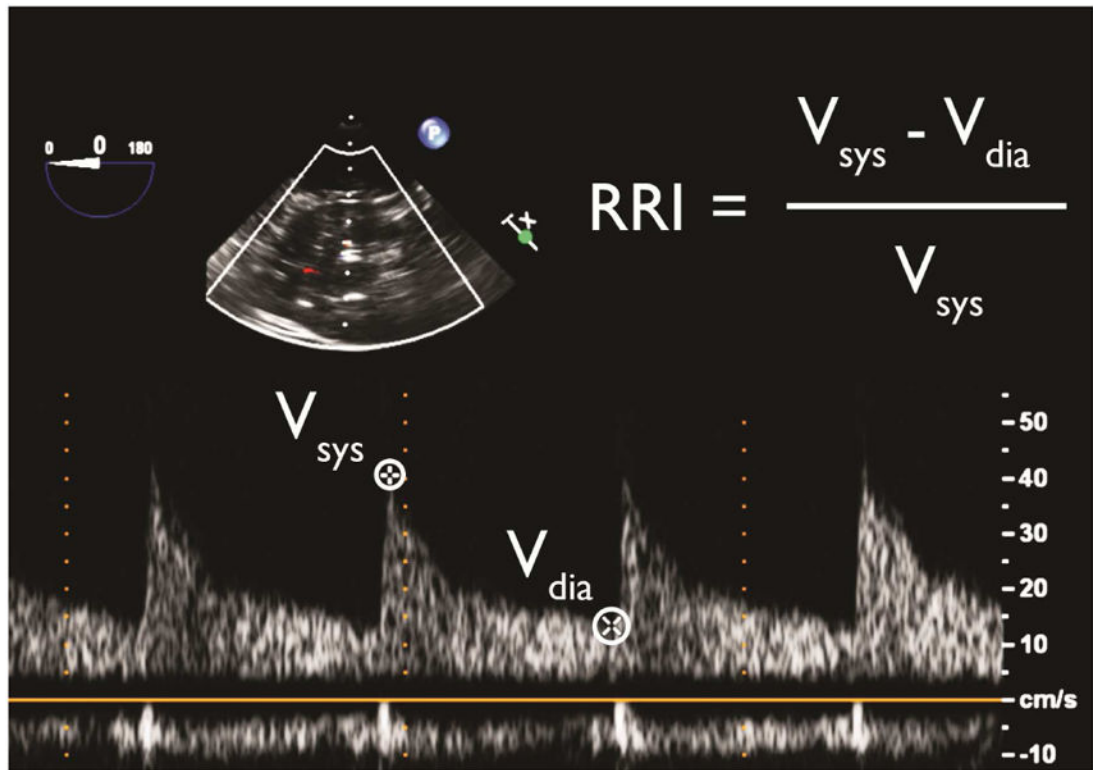
Figure 1.
Calculation of renal resistive index (RRI) using transesophageal echocardiography. V_{dia}-trough diastolic velocity, V_{sys}-peak systolic velocity.

Pre-CPB Renal Doppler Images
(n = 302)

Excluded* (n = 127):
• Irregular rhythm (n = 7)
• Creatinine clearance < 60 mL/min (n = 53)
• High beat-to-beat variability (n = 65)
*For one or more criterion

Images Available for Analysis
(n = 175)

Normal
Aortic Valve
(n = 115)

Aortic
Insufficiency
(n = 16)

Aortic
Insufficiency / Stenosis
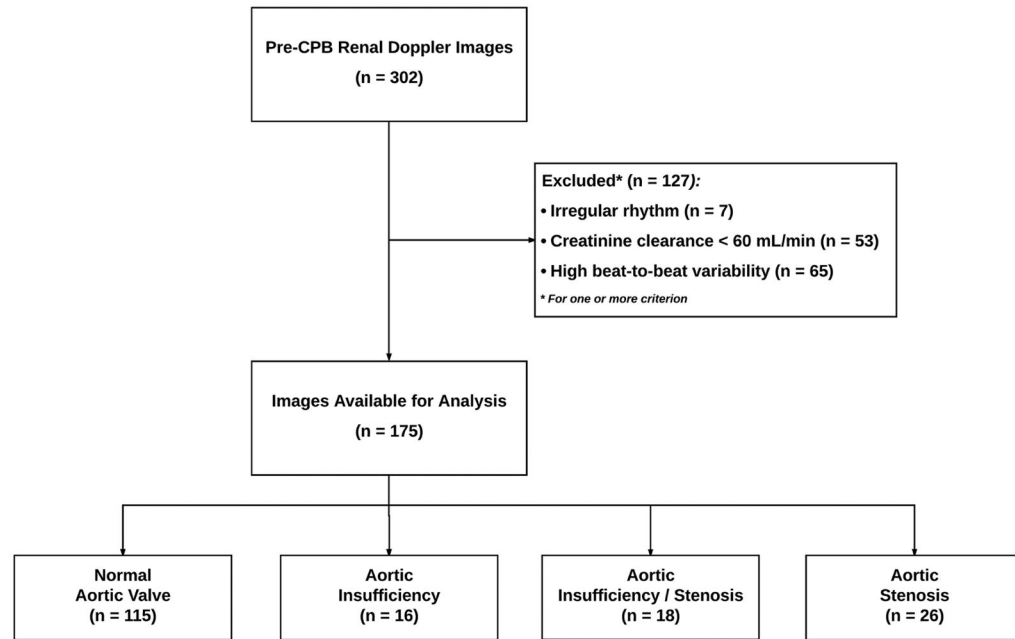(n = 18)

Aortic
Stenosis
(n = 26)

Figure 2.
STROBE study population flow-chart. Abbreviations: CPB-cardiopulmonary bypass.
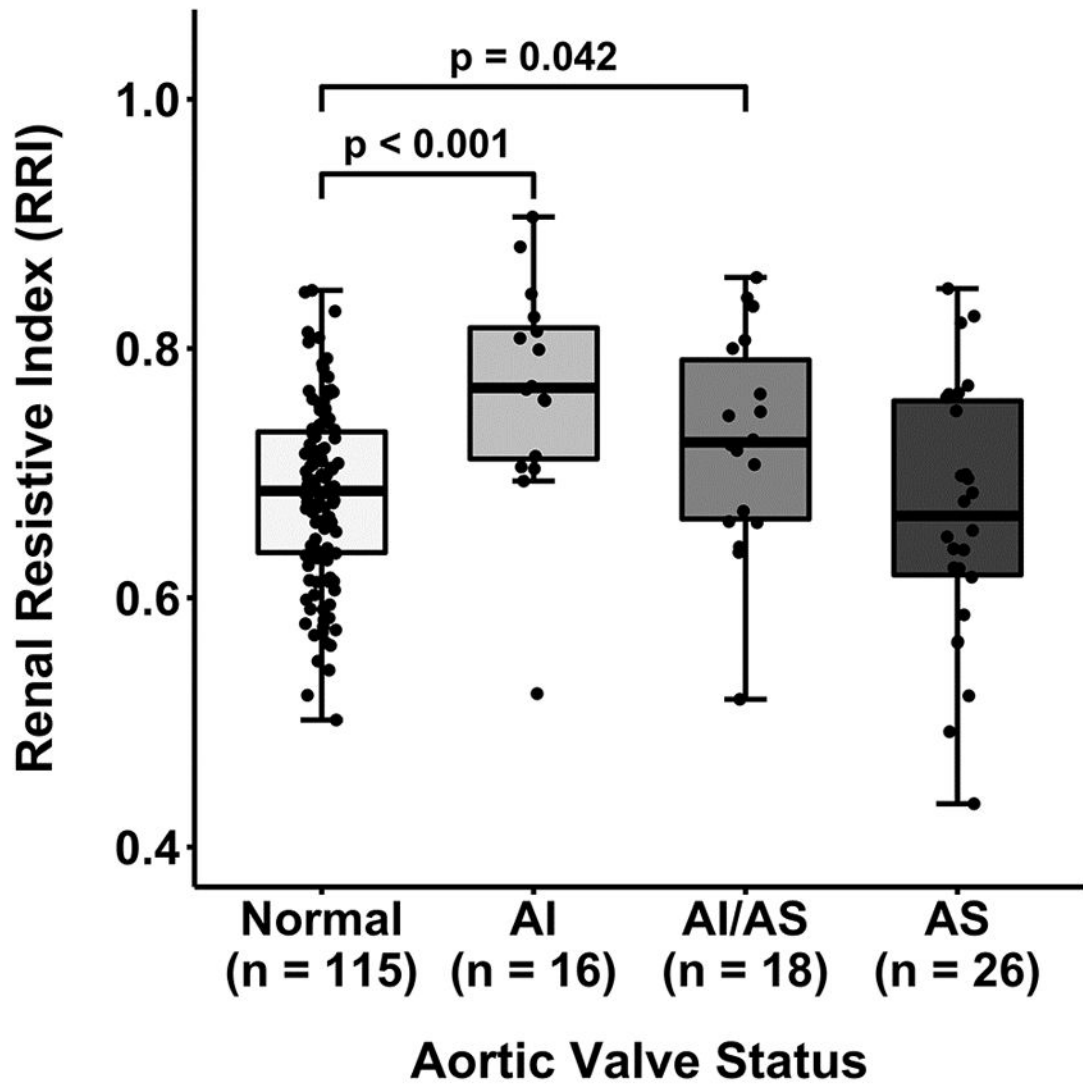
Figure 3.
Renal resistive index determined prior to cardiopulmonary bypass stratified by aortic valve status. P-values represent corrected post-hoc comparisons. Additional differences: AI vs. AS (p=0.013). AI-aortic insufficiency, AI/AS-combined aortic insufficiency/stenosis, AS-aortic stenosis.

Figure 4.
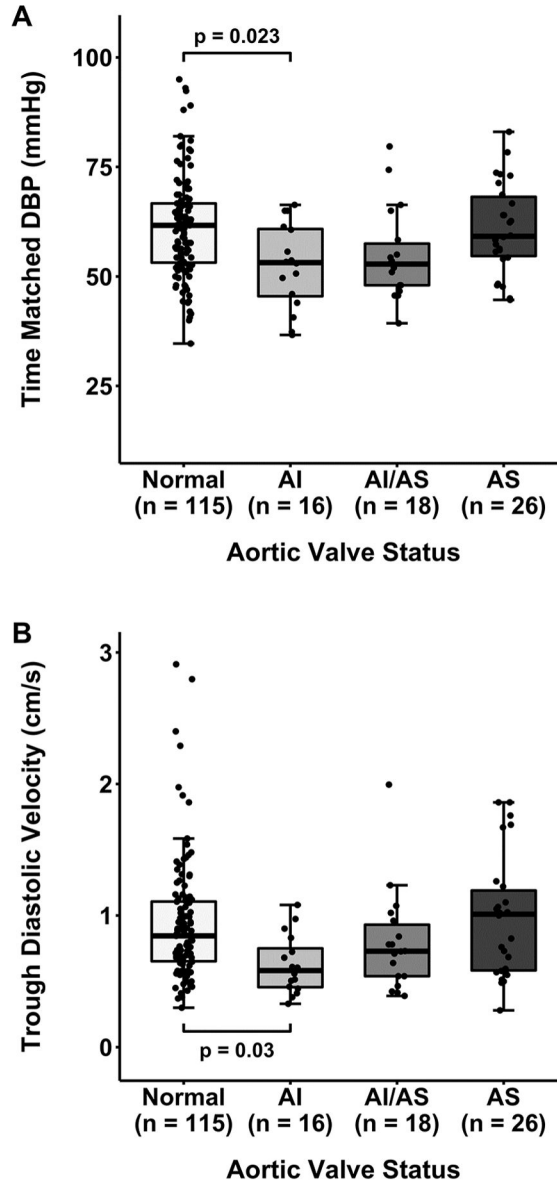Diastolic blood pressure (A) and trough diastolic velocity (B) at time of RRI determination, stratified by aortic valve status. P-values represent corrected post-hoc comparisons. Additional differences: diastolic blood pressure (p=0.035), trough diastolic velocity (p=0.03) in AI vs. AS. AI-aortic insufficiency, AI/AS-combined aortic insufficiency/stenosis, AS-aortic stenosis, DBP-diastolic blood pressure.
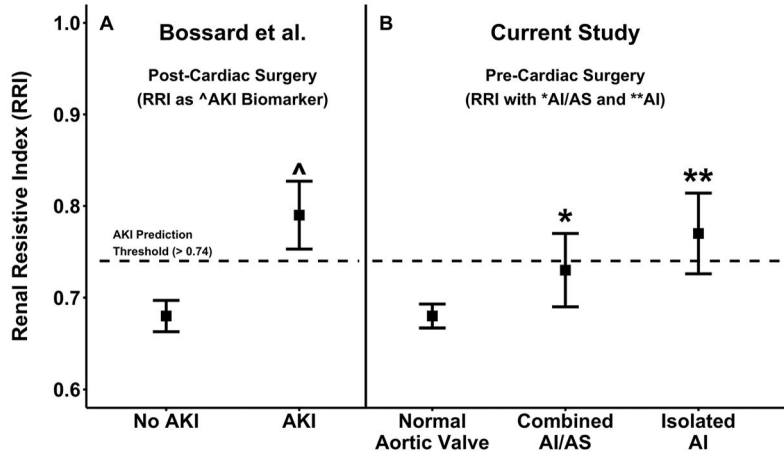
Figure 5.
Renal resistive index (mean±95% CI) for cardiac surgery patients in two studies. Values from (A) Bossard et al., [3] stratified by AKI status and determined postoperatively by transabdominal ultrasound and (B) the current study, stratified by aortic valve status, determined prior to CPB. Notably, *pre*-intervention values in the AI and AI/AS subgroups from the current study considerably overlap *post*-intervention values in the AKI subgroup. The horizontal hatched line reflects the RRI threshold (>0.74) for AKI prediction developed by Bossard et al. AI-aortic insufficiency, AI/AS-combined aortic insufficiency/stenosis, AKI-acute kidney injury.

Table 1

Patient and Procedural Characteristics

	Aortic Valve Status				
	Normal (n=115)	Insufficiency (n=16)	Insufficiency & Stenosis (n=18)	Stenosis (n=26)	p-value
Demographics and Comorbidities					
Age (years)	58 (48–66)	64 (49–69)	67 (61–76)	68 (65–76)	<0.0001
Female	38 (33%)	6 (38%)	6 (33%)	11 (42%)	0.83
Body Mass Index	30 (28–34)	31 (28–32)	28 (26–35)	30 (26–34)	0.76
Diabetes	34 (30%)	5 (31%)	3 (17%)	5 (20%)	0.53
Hypertension	53 (46%)	12 (75%)	9 (50%)	13 (52%)	0.20
Proteinuria	8 (7%)	1 (6%)	1 (6%)	4 (15%)	0.50
Stroke	5 (4%)	0 (0%)	3 (17%)	1 (4%)	0.12
Peripheral Vascular Disease	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0.66
Left Ventricular Ejection Fraction					0.005
<45%	25 (22%)	2 (12%)	1 (6%)	3 (12%)	
>55%	49 (43%)	12 (75%)	15 (83%)	18 (72%)	
45–55%	41 (36%)	2 (12%)	2 (11%)	4 (16%)	
Procedural Characteristics					
Procedure					<0.0001
Aortic	3 (3%)	0	0	0	
CABG	59 (51%)	2 (12%)	0	0	
Combined	6 (5%)	11 (69%)	7 (39%)	9 (35%)	
Other	19 (17%)	0	0	0	
Valve	28 (24%)	3 (19%)	11 (61%)	17 (65%)	
CPB Time (minutes)	142 (105–194)	168 (141–196)	138 (122–213)	155 (121–172)	0.19
Cross Clamp Time (minutes)	73 (32–102)	117 (105–138)	103 (82–141)	94 (88–117)	<0.0001
Baseline Hemodynamics					
Systolic Blood Pressure (mmHg)	142 (127–166)	155 (143–169)	132 (117–160)	144 (132–166)	0.35
Diastolic Blood Pressure (mmHg)	64 (57–72)	51 (46–60)	60 (47–70)	66 (54–71)	0.027
Pulse Pressure (mmHg)	77 (64–94)	92 (81–104)	76 (64–90)	81 (68–96)	0.094

| | Aortic Valve Status | | | | |
	Normal (n=115)	Insufficiency (n=16)	Insufficiency & Stenosis (n=18)	Stenosis (n=26)	p-value
Mean Arterial Pressure (mmHg)	90 (80–100)	88 (75–97)	89 (73–105)	90 (84–106)	0.75

CABG-coronary artery bypass grafting, CPB-cardiopulmonary bypass. Values represent median (Q1–Q3) or frequency (%).

Table 2

Renal Characteristics

| | Aortic Valve Status | | | | |
	Normal (n=115)	Insufficiency (n=16)	Insufficiency & Stenosis (n=18)	Stenosis (n=26)	p-value
Baseline Serum Creatinine (mg/dL)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.7–1.1)	0.59
Baseline Creatinine Clearance (mL/min)	98 (82–125)	91 (71–124)	86 (74–95)	86 (80–100)	0.030
Maximum Postoperative Creatinine (mg/dL)	1.2 (1.0–1.4)	1.6 (1.1–1.9)	1.1 (1.0–1.4)	1.1 (1.0–1.4)	0.045
Maximum Creatinine Increase (%)	20.0 (8.3–50.0)	47.3 (20.4–78.1)	23.6 (11.5–39.6)	23.6 (0.0–48.2)	0.14
KDIGO AKI	56 (49%)	12 (75%)	9 (50%)	14 (54%)	0.27
KDIGO Stage					0.25
0	59 (51%)	4 (25%)	9 (50%)	12 (46%)	
1	46 (40%)	8 (50%)	9 (50%)	11 (42%)	
2	6 (5%)	1 (6%)	0 (0%)	1 (4%)	
3	4 (3%)	3 (19%)	0 (0%)	2 (8%)	

KDIGO-Kidney Disease: Improving Global Outcomes, AKI-Acute Kidney Injury. Values represent median (Q1–Q3) or frequency (%).

Table 3

Doppler and Hemodynamic Parameters Prior to Initiation of Cardiopulmonary Bypass

| | Aortic Valve Status | | | | |
	Normal (n=115)	Insufficiency (n=16)	Insufficiency & Stenosis (n=18)	Stenosis (n=26)	p-value
Doppler Parameters					
Renal Resistive Index	0.69 (0.64–0.73)	0.77 (0.71–0.82)	0.72 (0.66–0.79)	0.67 (0.62–0.76)	0.0003
Peak Systolic Velocity (cm/s)	2.81 (2.16–3.50)	2.71 (2.03–3.28)	2.54 (2.03–3.56)	3.15 (2.15–4.12)	0.87
Trough Diastolic Velocity (cm/s)	0.84 (0.65–1.11)	0.58 (0.46–0.75)	0.73 (0.54–0.93)	1.01 (0.58–1.19)	0.006
Time-Matched Hemodynamic Parameters					
Heart Rate (bpm)	69 (60–81)	72 (67–83)	71 (68–82)	70 (61–82)	0.57
Systolic Blood Pressure (mmHg)	120 (105–132)	113 (107–123)	113 (97–139)	120 (103–135)	0.80
Diastolic Blood Pressure (mmHg)	62 (53–67)	53 (46–61)	53 (48–58)	59 (55–68)	0.007
Pulse Pressure (mmHg)	58 (49–68)	60 (50–74)	50 (47–85)	56 (49–66)	0.92
Mean Arterial Pressure (mmHg)	80 (71–88)	73 (67–81)	79 (67–88)	81 (71–93)	0.24

Bpm–beats per minute. Values represent median (Q1–Q3) or frequency (%).